Paraneoplastic syndromes in patients with ovarian neoplasia

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Summary
The prevalence of several paraneoplastic syndromes associated with ovarian cancer was determined from a clinicopathological study of 908 patients with primary ovarian malignancy in the North East Thames Region. The diversity and rarity of these manifestations are great and the explanation for them is difficult. Circumstantial evidence suggests that in some cases an autoimmune phenomenon is the most plausible cause.

Introduction

Paraneoplastic syndromes are systemic manifestations of cancer that cannot readily be explained by the local or metastatic effects of a tumour or of hormones indigenous to the tissue in which the tumour arises. The syndromes fall into four broad groups, in which the patient has endocrine, neurological, haematological/vascular, or dermatological disease. Ovarian cancer, itself notable for the diversity of the pathological manifestations of the primary tumour and its metastases, features widely in descriptions of paraneoplastic syndromes.

Endocrine manifestations as a consequence of oversecretion of the normal ovarian hormones by ovarian tumours should not, by definition, be included in the category of paraneoplastic or para-endocrine syndromes[1]. Certain ovarian germ cell tumours produce chorionic gonadotrophin and α-fetoprotein[2]; there are no clinical manifestations apart from formation of theca lutein cysts in the normal contralateral ovary.

Some paraneoplastic syndromes are associated with so-called collagen disease, for which there may be an established or theoretical immunological basis[3]. Antibodies to a number of tissue antigens have been identified in patients with ovarian cancer[4-6]. Circulating immune complexes have also been demonstrated in the sera of patients with metastatic epithelial ovarian cancer[7] and the nephrotic syndrome that occurs in some patients with ovarian cancer has been attributed to glomerular deposition of immune complexes[8]. One of the most striking demonstrations of the autoimmune basis of a paraneoplastic syndrome is that in certain patients with ovarian carcinoma, expression of a particular type of Purkinje cell antibody is associated with subacute cerebellar degeneration[9,10]. It has been suggested that assay of these antibodies may be a useful tumour marker[11,12]. This paper reports the results of a study of the data at presentation of 908 patients with primary epithelial ovarian cancer, collected prospectively in the North East Thames Region.

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Data source

In the 1970s a data bank for ovarian cancer in the North East Metropolitan Region was set up by the Association of Obstetricians and Gynaecologists of the Region in association with the Regional Histopathologists Group. Data was entered either by pathologist or clinician, and as soon as a case was notified, the clinical data on an agreed proforma were obtained from the surgeon concerned - he/she provided details of the mode of presentation, investigation, operative staging, and treatment. Histological material was reviewed centrally by two of the authors. The Regional Histopathologists Group established a reference panel for review of difficult, unusual, and interesting cases. Whenever possible, the review panel was provided with unstained sections so that special stains could be examined. This report covers the clinical history, the clinical features at presentation, and the histological findings in 908 patients with primary ovarian cancer.

Method

The proforma sent to clinicians asked for data on chronic medical conditions, long-standing medication, previous cancer, and relevant family history. Other data were obtained from the clinical examination at presentation and from the laboratory and radiographic investigations, including features such as evidence of thrombophlebitis, venous obstruction, or polycythaemia. Although this was a prospective study, completeness of the initial data collected varied between individuals and with the circumstances of presentation. An associated medical condition was found in just over a third of patients.

Results

Table 1 lists the medical conditions most commonly reported or found on examination. There was no

Table 1. North East Metropolitan Region ovarian cancer study

Cases of primary ovarian cancer	908
Chronic medical disorders including:	245
Hypertension	39
Respiratory	22
Thyroid	20
Cardiac	20
Gastrointestinal	14
Diabetes	12
Osteoarthritis	11
Psychiatric	10

Table 2. Possible para-neoplastic syndromes

Collagen disorders	
Dermatomyositis	1
Polyarteritis nodosa	1
Rheumatoid arthritis	8
Reflex sympathetic dystrophy	0
Other skin manifestations	0
Neurological	
Cerebellar degeneration	1
Haematological	
Polycythaemia	1
Pre-existing thrombosis/thrombophlebitis	7
Haemolytic anaemia	0
Para-endocrine	
Hypercalcaemia	0

recorded history of a chronic medical condition in the other patients, and so, by implication, no pre-existing symptomatic paraneoplastic syndrome. It is recognized that there was an inherent tendency to under-reporting. From these data it was possible to prepare a list of conditions that might be considered to form part of a paraneoplastic syndrome (see Table 2). Some are so common that a coincidental relationship might be anticipated. Of the other chronic medical conditions reported, thyroid disease occurs with surprising frequency. The significance of this association is unknown[13].

Haematological conditions

The figures given for the prevalence of venous involvement include venous obstruction from extrinsic compression due to pelvic tumour, as well as spontaneous iliofemoral thrombosis, as distinction between these was not possible in many cases. Ovarian malignancy may be silent even when it presents with venous gangrene[14]. Of the patients in this series with vascular problems, a diagnosis of thrombophlebitis migrans in one prompted a gynaecological consultation which brought to light an unsuspected ovarian malignancy[15]. This was clearly a paraneoplastic phenomenon, but in other cases a thrombotic tendency may have been operating as a paraneoplastic process. One other patient with a haematological disorder was found; she had secondary polycythaemia with a haemoglobin concentration of 16 g/dl. The tumour in this instance was a well differentiated mucinous adenocarcinoma that had arisen between the leaves of the broad ligament. It is at this site that leiomyomas have been reported to have a similar haematological effect[16]. It may be that this is due to excessive production of erythropoietin by the kidney secondary to a pressure effect on the ureter; tumours in this site are too remote from the kidney to have a direct vascular effect but there is no convincing explanation for why this effect should be confined to tumours between the leaves of the broad ligament and not from any other form of pelvic impaction. Ectopic erythropoietin production has been reported as a true paraneoplastic phenomenon[17].

Neurological conditions

There was one patient in this series who developed cerebellar degeneration in the presence of recurrent ovarian cancer. From the time scale this was almost certainly a paraneoplastic event, though no studies for Purkinje cell antibodies were carried out. Other neurological phenomena such as neuromyopathy[9] were not found.

Osteoarticular disease

Of the collagen disorders, rheumatoid arthritis has been described as occurring as a paraneoplastic syndrome. In none of the cases recorded here for which sufficient detail was made available was it possible to postulate a temporal relation with the progress of the disease. Systemic sclerosis and dermatomyositis have a much stronger relationship with underlying visceral malignancy, including ovarian cancer[18] and in this series the two patients with dermatomyositis and polyarteritis may be considered to have had a paraneoplastic condition.

Reflex sympathetic dystrophy (shoulder-hand syndrome) in association with endometrioid ovarian cancer has been shown to antedate the clinical detection of the cancer[19]. It is unlikely that the presence of palmar fasciitis (Dupuytren's contracture), which is characteristic of this paraneoplastic syndrome, would have been recorded in the routine clerking of gynaecological patients and so would not have been recorded as a chronic medical disorder. Any such case would have been overlooked.

Dermatological conditions

During the period of study there were no dermatological manifestations of paraneoplastic syndromes other than dermatomyositis recorded, though shortly before the study started a patient who presented with endometrioid ovarian carcinoma later developed acanthosis nigricans and metastatic carcinoma, a previously reported association[20,21]. These data suggest that apart from venous complications (many of which may have been from mechanical causes rather than from a paraneoplastic coagulopathy) and rheumatoid arthritis (which is of doubtful relevance), the prevalence of individual paraneoplastic syndromes in association with malignant ovarian disease is of the order of only one in 1000.

Discussion

Because the prevalence of paraneoplastic syndromes is so low few gynaecologists, even those in specialist oncological practice, will encounter them. The syndromes will tend, therefore, to be diagnosed by consultants in dermatological, endocrine, neurological and other specialties to whom the patient may be referred, and in some cases will precede the diagnosis or even suspicion of cancer. Inappropriate secretion of hormones is the subject of much continuing study. Ectopic secretion of ACTH by bronchial carcinoma is well recognized, but it has also been reported that neoplasms of the ovary can cause Cushing's syndrome[22] and secrete polypeptide hormones such as gastrin[23], parathyroid-hormone-like substances[24], insulin-like substances[25] and smaller active molecules such as serotonin[26] and amylase[27].

The effects of hormone secretion are often subclinical. The sera from some of the patients in this series were screened for cortisol and ACTH, but both were within the reference range (Rees L, personal communication). Hypercalcaemia has been recorded particularly in cases of small cell carcinoma of ovary[28], and also in clear cell carcinoma[29], mucinous cystadenocarcinoma[30], serous cystadenocarcinoma[31], and epidermoid carcinoma[32]. It is unlikely that the data at presentation or follow up would have identified hypercalcaemia in our cases.

Patients with gynaecological cancers may develop cerebellar degeneration and serum antibodies to Purkinje cells. In one report, the finding of a particular type of Purkinje cell antibody in women

with cerebellar damage was the sole indication for laparotomy to look for gynaecological cancer; this was because of the known association between these antibodies and neoplasia, particularly of the female genital system and breast. These antibodies are not found in patients with cerebellar degeneration related to oat cell carcinoma of the lung, and only one of the 38 women with Purkinje cell antibodies that Hetzel *et al.*[11] studied did not have cancer. Plasmapheresis has been successfully used as therapy[33].

Of all tumours, ovarian cancer is clearly one of the more immunogenic. A cell mediated immune response that can be blocked by serum factors has been demonstrated[34,35] though attempts to manipulate this response for therapeutic purposes have had only limited success. Auto-antibodies to normal tissues, including those of the female genital system, have also been identified in the sera of patients with ovarian cancer[4,6]. There may therefore be an immunological basis for some of the paraneoplastic syndromes. The demonstration of a relation between disease state and circulating immune complexes could be especially relevant[35]. Some of the haematological, neurological, renal and arthropathic manifestations may be explained on this basis. What is difficult to explain is the rarity of each of them as demonstrated in this report, there being only isolated examples in almost 1000 cases.

In conclusion, although paraneoplastic syndromes form only a small part of the protean manifestations of ovarian neoplasia, this disease is another example of how gynaecological disorders are relevant to a wide range of specialists from dermatologists to colorectal surgeons. Ovarian cancer is a disease of general relevance and not simply a problem for the specialist gynaecologist.

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